Total Mesorectal Excision: What Are We Doing?

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ABSTRACT

The introduction of total mesorectal excision (TME) for rectal cancer has reduced local recurrence rates and improved oncologic outcomes, although complication rates such as anastomotic leak have also been a consequence. With the advent of neoadjuvant therapy for rectal cancer, many are questioning how this development may change the role of TME. This review presents a history of how TME evolved and a description of this technique. Complication rates, the impact of neoadjuvant therapy on local recurrence, variations of TME such as nerve-sparing proctectomy and cancer-specific mesorectal excision, and a review of functional outcomes for various methods of reconstruction are presented.

KEYWORDS: Total mesorectal excision, rectal cancer, recurrence, surgical technique, review article

Objectives: At the conclusion of this article, the reader should be familiar with the technique of total mesorectal excision (TME); the results of clinical trials incorporating neoadjuvant treatments with TME; and the complication rates and functional outcomes seen with various reconstructive methods following TME.

Rectal cancer is one of the most challenging problems encountered by colorectal surgeons and is currently the second leading cause of cancer deaths in western countries. According to data collected from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program,[1] colorectal malignancies are fourth in overall frequency of cancers in the United States, with over 56,000 cancer-related mortalities recorded in 2002. Although mortality is generally related to the systemic spread of disease prior to surgical treatment, locoregional recurrence after proctectomy may be largely related to surgical technique and is responsible for considerable morbidity. This problem has been the focus of much attention over the past decade. Local recurrence rates of 30% or greater have been seen in some older series;[2] however, recent efforts to reduce the risk of local recurrence have resulted in rates of $< 10\%$ being commonly reported. Clearly, the widespread adoption of neoadjuvant therapy has been pivotal in improving local recurrence rates, but an equally important advance has been the improvement in surgical technique created by a clearer understanding of the local spread of rectal cancers. Modern proctectomy for rectal cancer is based on a sharp, meticulous extirpation of the cancer en bloc with its surrounding perirectal lymphatic tissue contained within a thin fascial layer, referred to as total mesorectal excision (TME). In this article, we will review the history of TME, including how it came to be known by this name. The proper technique for TME will be described, and the results of specific clinical trials regarding TME and its relationship to neoadjuvant therapy and local recurrence rates will be surveyed.

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Additionally, postoperative complications and their relationship to TME will be discussed.

HISTORY

Chapuis[3] provides an excellent review on the history of rectal anatomy and an etymological discussion of the term *mesorectum*. The author points out that the first known description of the mesorectum was by the Romanian surgeon and anatomist Thoma Jonnesco, though Jonnesco did not refer to the perirectal tissue by this name. Poirier and Charpy initially published Jonnesco's findings in 1896 in their multivolume reference *Traite d'Anatomie Humaine.* Jonnesco's descriptions remained almost unchanged in the second edition of that book, which was published in 1901,[4] attesting to the originality of his observations. Gerota[5] and Waldeyer[6] also referenced Jonnesco's writings in their monographs on rectal anatomy. Jonnesco was the first to observe that the rectum was encapsulated within a thin fibrous sheath, which partitions it from the other pelvic organs, and he also described how proper respect for this fibrous sheath allowed the rectum to be mobilized from the sacrum without damage to the presacral vessels.[3]

Although Heald was the first to promote total mesorectal excision,[7] Abel first described the procedure in 1931.[8] However, it was Heald who was instrumental in giving TME widespread attention in 1979,[9] reporting his institution's experience at North Hampshire Hospital in Basingstoke, England. In his article, he described important steps in performing proctectomy for cancer, including an emphasis on direct vision and sharp dissection that removes the mesorectum by remaining between the visceral and parietal pelvic fascia during mobilization of the rectum. Contemporary surgeons often protest that this technique was practiced prior to it being christened by Heald as *total mesorectal excision*. Although this may be true, Heald's article was still an important first step in creating a formal approach to proctectomy for cancer, reporting recurrence rates so low as to demonstrate why violation of this anatomic plane is unacceptable in oncologic surgery. Heald, in fact, reported the lowest recurrence rates for rectal cancer at that time, with his first series of 112 patients[2] showing a cumulative 5-year local recurrence rate of 2.7% and an overall corrected 5-year survival of 87.5%. Some have questioned the validity of Heald's extraordinary results;[10] nevertheless, more recent series[11,12] with comparable numbers of patients have reported similar recurrence rates and therefore lend support to Heald's earlier findings. Heald's publication helped lead to the introduction of TME as a standard surgical technique[13] for this operation, and has influenced how the technique for a proctectomy for cancer is taught throughout the world.

SPHINCTER PRESERVATION OR ABDOMINOPERINEAL RESECTION?

Survival is the highest goal of cancer treatment; however, outcome is determined by many factors that are not controllable by the operation performed. The biological behavior of the cancer and the cancer's stage at presentation are important prognostic factors that are predetermined before consultation with a surgeon and are thus unaffected by technique. Prevention of local recurrence and its resultant morbidity, however, is within the purview of proper patient selection and the surgical approach. With control of local recurrence in mind, the surgeon must decide whether the patient is a candidate for a sphincter-preserving resection. The question of who is a candidate for this approach varies among surgeons, but there are contraindications to sphincter preservation that all surgeons would agree on. No attempt at a sphincter-saving operation should be undertaken before determining whether the cancer involves the anal sphincter. If the cancer spares the sphincter, then assessing the patient's sphincter function would be the next logical step. Additionally, there are patients who are obese to the degree that the safe creation of an anastomosis cannot be performed.

The preoperative evaluation should start with a thorough history and physical exam, with special attention on the anorectal examination as a crucial part of the assessment. The anorectal examination should include a digital rectal exam (DRE) and rigid proctoscopy to precisely measure the distance of the tumor from the anal verge. An abdominoperineal resection (APR) is mandatory if there is no space between the tumor and sphincter mechanism on DRE, if the tumor is growing into the sphincter, or if the tumor is fixed to the pelvic floor. If there is a demonstrable separation between the cancer and the sphincter then a coloanal anastomosis may be considered from an oncologic standpoint. Transrectal ultrasound (TRUS) is used to further define the size of the tumor, involvement of adjacent organs, and depth of invasion. TRUS has been shown to be very accurate in assessing the T stage of the disease, with an accuracy of 80 to 95%[14,15] compared with computed tomography (CT; 60 to 75%) and traditional magnetic resonance imaging (MRI; 75 to 85%).[16–18] Any tumor involvement of surrounding structures, such as the prostate and seminal vesicles in men or the vagina in women, weighs heavily against a restorative procedure, although it is not an absolute contraindication. The value of TRUS in assessing N stage is limited, with accuracies that range from 70 to 75%.[14,15,18] These series show that TRUS is able to determine whether lymphadenopathy is present, but is inaccurate in revealing the nature of the lymphadenopathy (inflammatory/reactive versus neoplastic).

Sphincter-preserving surgery for rectal cancer was initially viewed with a jaundiced eye by many surgeons,

based on the belief that APR offered the greatest chance for disease-free radial and distal margins. Though it is accepted that a clear radial margin is necessary for curative surgery (hence the advantage of TME over other surgical approaches), how large of a radial margin that is required is unknown. A recent study selecting 656 nonirradiated patients[19] from the Radiotherapy + TME trial in the Netherlands found that a radial margin ≤ 2 mm was associated with a local recurrence risk of 16% compared with 5.8% in patients with a larger radial margin. Margins that were ≤ 1 mm were associated with an increased risk of distant metastasis (37.6 versus 12.7%) and shorter overall survival. These differences were of statistical significance. Distal margin have been further clarified as this issue has been revisited because of the popularization of TME. The requirement of a 5-cm margin requirement has been loosened. Several studies, including those by Paty et al[20] and Vernava and Moran,[21] suggest that there is no difference in survival or recurrence rates with a <2-cm distal margin as compared with a >2-cm margin. The envelope has been pushed even further by those asking whether any length of distal margins, no matter how slim, would be acceptable. Several series have shown that the distal intramural spread of cancer is rarely >1 cm,[22–24] but the previously mentioned study by Vernava and Moran clearly demonstrated reduced survival rates and increased rates of anastomotic recurrence with distal margins ≤ 8 mm. On balance, the current data would suggest that if the estimated distal margin of resection is <1 cm from the sphincter mechanism, then an APR should be chosen to avoid leaving residual disease behind.

Patients who have problems with incontinence should have a frank discussion with their surgeon about undergoing an abdominoperineal resection (APR). Compared with the worsening continence problems created by an inappropriately placed coloanal anastomosis, patients with major continence issues will have a better quality of life with a permanent stoma. Indeed, life with a properly placed permanent stoma is much better than patients may initially realize, as patients often have inaccurate preconceived notions about the limitations a stoma imposes. Having the patient undergo preoperative stoma counseling with an enterostomal therapist has been shown to improve patient's satisfaction with their surgery in the postoperative period.[25] Patients who have lesser problems with continence may be candidates for a sphincter-preserving operation, but they should be made aware of several points. Bowel function with a coloanal anastomosis will be erratic for at least several months after surgery, with frequent loose bowel movements as often as five or more times a day. Additionally, function may further deteriorate both with time as well as with adjuvant radiation therapy, and patients may have difficulty maintaining adequate hydration and making it to the facilities in time if their condition is hindered by medical problems. Creation of a pouch or a coloplasty can help partially mitigate this, as can dietary changes with increased fiber. Antimotility agents may play a supporting role. Expectations must be realistic in the preoperative discussion as they affect the patient's idea of what constitutes a "successful" surgery.

TECHNIQUE

Prior to the patient's arrival to the operating room, an enterostomal therapist should mark potential stoma sites, but a thorough review of the principles of stoma formation is beyond the scope of this article. The latest edition of Kirsner's *Inflammatory Bowel Disease* textbook offers an excellent chapter[26] on the benefits of preoperative consultation with enterostomal therapy, and outlines important considerations for placing and creating the stoma to allow for independent care by the patient. Although the need for mechanical bowel preparation has recently been questioned, this is currently the practice of the majority of surgeons and should remain the standard until better studies are produced. Sequential compression devices (SCDs) should be activated prior to the induction of general anesthesia, as this is a common point when deep venous thrombosis (DVT) occurs. Intravenous antibiotics that have broad activity against Gram-negative and anaerobic bacteria should be infused less than one hour prior to the skin incision for maximal benefit[27,28] in preventing surgical site infections. Although the early postoperative use of subcutaneous heparin and fractionated heparins has been shown to be beneficial in preventing DVT[29] when compared with SCD use alone, their preoperative use has been more controversial. Several studies have shown an increased rate of hemorrhage without a clear benefit in preventing DVT[30] when compared with their early postoperative administration.

The patient is placed in the modified-lithotomy position, a Foley catheter is inserted, and the rectum is irrigated with both saline and a tumoricidal solution such as povidone iodine. Ureteral stents are placed if indicated. Studies demonstrate that TME can be performed laparoscopically[31,32]; however, in the hands of surgeons with advanced laparoscopic skills, the following description of TME will focus on the proper planes of dissection, which should be the same whether the approach is open or minimally invasive.

The goal of this surgery is the en bloc resection of the rectal cancer with a complete pararectal lymph node dissection as contained in the mesorectum. Any additional lymphadenopathy may also be dealt with depending on the stage of the tumor. One overarching principle for oncologic proctectomy is that any dissection of the rectum must be performed sharply. This not only prevents disruption of the mesorectum and thus iatrogenic tumor spread, but sharp dissection is also part of a

meticulous and exact approach that identifies every important adjacent structure and avoids inadvertent injury to the patient. Blood loss will often be less with this approach. Blunt distraction of tissue in cancer surgery of the rectum produces worse outcomes via haphazard circumferential margins, where the imprecise distraction of tissue rather than sound surgical principles determines the extent of resection.

The focus of the operation is achieving a complete resection of the cancer with adequate radial and circumferential margins. To reach this goal, the lateral dissection of the rectum must not breech the fascia propria of the rectum, staying outside the mesorectum. The rectum must also be mobilized anteriorly and posteriorly to ensure an adequate distal margin, which includes sharp dissection through Denonvilliers' and Waldeyer's fascia.

The peritoneal cavity is entered through a generous midline incision. A thorough exploration for evidence of metastatic disease is performed including bimanual palpation of the liver; routine intraoperative liver ultrasound is not utilized. The pelvis is also assessed to ensure resectability of the primary tumor. In the absence of large-volume metastatic disease or an unresectable primary, the abdominal phase of the resection is begun. Attention is first turned to the lateral attachments of the descending and sigmoid colons. An incision is made along the lateral peritoneal reflection ("white line of Toldt") and the embryonic plane between the colonic mesentery and retroperitoneum is entered. This is an avascular plane that can be quickly developed using a combination of upward traction on the left colon, lateral traction on the retroperitoneal tissues, and sharp dissection. The left ureter is identified and swept laterally. The mobilization of the left colon mesentery should proceed toward the midline until the periaortic tissues are encountered. At this point, attention is turned to mobilization of the splenic flexure. The omentum is separated from the distal half of the transverse mesocolon by entering the lesser sac and carrying the dissection down to the base of the mesentery. Likewise, the lateral dissection is continued cephalad and around the splenic flexure to divide the phrenocolic and splenocolic ligaments completely. With the left colon now completely mobilized to the midline, the inferior mesenteric artery (IMA) is identified at its origin from the aorta. The position of the left ureter is again confirmed as it is extremely vulnerable at this stage of the procedure. The IMA is then divided and ligated at this point, taking care to preserve the small nerve fibers of the preaortic sympathetic/superior hypogastric plexus. These nerves should be cleared from the inferior mesenteric artery by keeping the plane of dissection between the aorta and IMA flush with the posterior wall of the artery. The inferior mesenteric vein is also divided at this level. Next, the short left colic artery is dissected and its ascending and descending branches identified. The left colic artery proper is divided and ligated such that the communication between the ascending and descending branches of the artery is maintained. Dissection is then carried up to the edge of the distal descending colon along the course of the descending branch of the left colic artery. This will ensure good collateral blood supply to the anastomosis or colostomy from the middle colic artery. The marginal artery at this level is divided. If brisk arterial bleeding is encountered, the artery is ligated. The descending colon is then divided between bowel clamps. The inferior mesenteric vein can be ligated a second time just below the pancreas and the mesentery partially divided, preserving the marginal. This can be performed as a lengthening maneuver when a coloanal anastomosis is planned if necessary.

The pelvic phase of the operation is then begun. The plane immediately posterior to the IMA in the midline is developed sharply. This dissection is carried down over the sacral promontory and into the pelvis. The plane of dissection is between the presacral fascia and the investing fascia of the mesorectum. The hypogastric nerves should be identified at this point and preserved. Once they have been swept laterally out of harm's way, the lateral attachments of the rectum can be divided out close to the pelvic sidewall. This dissection is performed using electrocautery with the tissues held on stretch between the blades of a Kelly clamp. The anterior dissection is begun by incising the peritoneal reflection between the anterior wall of the rectum and the lower uterus or bladder. If the tumor is on the anterior wall of the rectum, the peritoneum should be incised anterior to the reflection as this will lead into the plane of dissection between Denonvilliers' fascia and either the vagina or seminal vesicles/prostate gland. This preserves a fascial boundary around the tumor, but may result in an increased incidence of injury to the parasympathetic nerves, which lie anterior to Denonvilliers' fascia. For posterior tumors, the plane of dissection begins posterior to the peritoneal reflection and is developed between the anterior rectal wall and Denonvilliers' fascia to minimize nerve injury. Once the rectum has been completely mobilized to the chosen point distal to the tumor, it is divided and the anastomosis created.

Heald's[33] experience offers practical advice to avoid nerve injury affecting the function of the genitalia. He states that the incision through Denonvilliers' fascia should be made in a U-shaped fashion to avoid damage to the anterolateral-lying neurovascular bundles that supply the seminal vesicles. As demonstrated by Lindsey et al,[34] Denonvilliers' fascia is more closely applied to the prostate than the rectum, and lies just anterior to the fascia propria and the proper plane of dissection. By not excising Denonvilliers' fascia, postoperative sexual dysfunction can be minimized without compromising the oncologic outcome of the surgery.

Whereas extending the dissection to the levators is necessary for mid and low rectal cancers, some[35] have questioned whether this should be done for rectosigmoid and high rectal cancers. Adrian and Long[35] opine that comparable oncologic results can be achieved with a wide resection of the affected portion of the mesorectum for these more proximal cancers. They emphasize incorporating adequate distal and radial margins, which they state should be 5 cm and >1 mm, respectively. By not resecting all of the mesorectum for upper-third rectal cancers, devascularization of the rectum distal to the anastomosis may be avoided. Using this technique, Adrian and Long[35] have achieved a relatively low anastomotic leak rate of 7.3%.

If the case of APR, the low rectum is not divided. Instead, the sigmoid stump is tagged with a metal ring which is placed into the presacral space, along with a closed-suction drain brought out through the skin of the lower abdomen. The omentum is mobilized and used to fill the pelvis to exclude the small bowel. The abdomen is then closed and the end-descending colostomy matured.

The patient is now turned into the prone jackknife position. The anus is closed with a pursestring suture to prevent extrusion of shed tumor cells. A diamond-shaped skin incision is made around the anus using the tip of the coccyx, both ischial tuberosities, and the midpoint of the perineal body as landmarks. The incision is deepened into the ischiorectal fossa by following the avascular plane between the sphincters and the perirectal fat. The levators are first divided posteriorly under the coccyx and then the incision is carried laterally. The metal ring previously placed in the presacral space is then retrieved and the proximal end of the specimen is brought out through the posterior perineal wound. The anterior dissection is completed under direct vision in a retrograde fashion. This provides excellent exposure and minimizes the risk of violating the tumor or injuring the distal ureters, prostate gland, or urethra. After the specimen has been removed, the deep tissues of the perineal wound are irrigated and closed with interrupted 0-vicryl figure-of-eight sutures. The skin is loosely approximated with vertical mattress stitches of 3–0 vicryl.

RESULTS

Heald and colleagues[36] reviewed their experience with TME at North Hamphsire Hospital in Basingstoke, England, over a period from 1978–1997. This large case series consisted of 519 surgical patients with histologically proven adenocarcinoma of the rectum located anywhere up to 15 cm from the anal verge. All patients had their surgery performed by Dr. Heald, thus standardizing the surgical approach. Surgeries included those with both curative and palliative intent. Preoperative radiation therapy was administered to 49 of the 519 patients. The Dukes distribution of the patients was as follows: 102 with Dukes A, 167 with Dukes B, 142 with Dukes C, and 108 with Dukes D disease (residual disease or metastatic disease). The operations performed consisted of 465 anterior resections, 37 APRs, 10 Hartman procedures, 4 local excisions, and 3 surgeries that revealed unresectable disease and therefore consisted of laparotomy and closure. A diverting stoma was made in 382 patients with the majority being closed within 2 months. A database was created to record information as patients were regularly followed in their postoperative period. Remarkably, only one patient was lost to follow-up.

Following anterior resection with curative intent, the 5-year survival rate was 81% and the 10-year survival rate was 80%. In this subgroup of patients, Dukes stage, tumor grade, anastomotic leak rates, location of the tumor and the location of the anastomosis did not affect local recurrence rates. However, extramural vascular invasion resulted in a statistically significant increase in local recurrence rates (9%) compared with local recurrence rates in patients without this finding (1%). Overall failure rates in this subgroup were affected by both vascular invasion and Dukes stage, but not other factors.

Cancer-specific survival among all 519 patients was 68% at 5 years and 66% at 10 years. Of those patients treated with curative intent, the cancer-specific 5-year survival was 80% and was 78% at 10 years. Analyzing the entire patient population, local recurrence rates were 6% at 5 years and 8% at 10 years. According to the specific surgery performed, local recurrence for anterior resections at 5 and 10 years was 5% compared with those undergoing APR, who had local recurrence rates of 17% at 5 years and 36% at 10 years ($p < 0.001$). The overall 5- and 10-year recurrence rates for patients undergoing anterior resection with curative intent were 2% out of 380 patients. No patient with metastatic disease survived beyond 5 years by the conclusion of the study. The clinically apparent anastomotic leak rate for anterior resections with curative intent was 6.5%, whereas an additional 5.5% of patients had leaks that were clinically silent, but were detected radiologically.

In discussing their results, the authors point out that adjuvant therapy was used in a small percentage of their patients and therefore had little affect on outcomes. Although trials studying the need for adjuvant therapy in the setting of TME are discussed below, one of Heald's conclusions was that adjuvant therapy might not be necessary with a properly performed TME. Also mentioned in the article were the uninspiring cure rates in patients undergoing APR. TME has decreased the rate of APR in many series, including Heald's, but in Heald's series TME only improved outcome in patients undergoing anterior resection. Why TME would not affect recurrence rates with APR is not clear, but the authors suggest that tumor implantation during the perineal portion of the surgery may be a reason. It is also known

that the fascial envelope of the low rectum thins considerably and may even be absent in the last 1 to 2 cm. This may allow the lowest rectal cancers, those typically treated by APR, to spread more readily into the pararectal tissues.

Queen Mary Hospital[37] in Hong Kong reported their results with 622 patients with rectal cancer treated by open anterior resection. Patients with mid or low rectal cancers were treated with TME; rectosigmoid and upper rectal cancers were treated with a cancer-specific or partial mesorectal excision (PME), where the rectum was transected 4 to 5 cm below the tumor. The median level of the cancer in this series was 8 cm from the anal verge. Surgery with curative intent was performed in 90.5% of patients (although 3 patients had histologically positive margins), with the remainder of the patients having a palliative procedure. A stapled anastomosis was created in 83.1% of patients. Of the 16.9% who had a hand-sewn anastomosis, 32 were coloanal and 73 were high colorectal anastomoses. The break down of all patients by stage was as follows: stage 0 = 0.8%, stage I = 16.1%, stage II = 36.7%, stage III = 38.4%, and stage IV = 8.5%. Radiation therapy was given to 42 patients, with half receiving preoperative radiation treatment.

TME was performed in 396 patients and PME in 226. TME was associated with longer operative times, higher blood loss, longer hospital stays and a higher incidence of stoma formation. The rate of anastomotic leaks was significantly higher with TME compared with PME (8.1 versus 1.3%). Furthermore, multivariate analysis revealed that TME, male gender, the absence of a stoma, and blood loss $>$ 500 mL were independent risk factors for anastomotic leaks. Yet the overall postoperative mortality (1.8%) and morbidity were not significantly different between patients undergoing TME or PME. Univariate analysis showed that a distal margin of $<$ 2 cm, perineural or lymphovascular invasion, stage of disease and creation of a coloanal anastomosis were significant factors predicting local recurrence. Based on multivariate analysis, the stage of disease and the presence of a coloanal anastomosis were associated with high rates of local recurrence. Actuarial 2-year and 5-year recurrence rates were 6.0% and 9.7%, respectively, and included both local recurrence and distant disease.

The median follow-up for patients who survived was 39.6 months. In all patients studied, 5-year overall survival was 66.5% and 5-year cancer specific survival was 74.5%. Multivariate analysis showed that tumor stage and the presence of lymphovascular and perineural invasion predicted decreased disease-specific survival. Due to longer operative times, higher anastomotic leak rates, a more technically demanding surgery and a higher incidence of stoma formation, the authors called for a more selective use of TME. The authors argue that oncologic outcome is not compromised with this approach based upon similar cancer-specific survival patterns between TME and PME in this study.

TME has produced superior local control of cancer as compared with nonstandardized surgery. Because of this dramatic improvement in local control reported by earlier studies, some have questioned whether (neo-) adjuvant radiation therapy is necessary to achieve acceptable local recurrence rates. A landmark study[38] was undertaken by the Dutch Colorectal Cancer Group to investigate the efficacy of preoperative radiotherapy in combination with TME for rectal cancer. Over the 3-year enrollment period, patients with histologically confirmed adenocarcinoma of the rectum no farther than 15 cm from the anal verge and who were without evidence of distant metastases were studied. Any patient with a fixed tumor or a tumor initially treated with local excision was excluded, as were patients with previous or coexisting cancers. Additionally, patients who had undergone prior large bowel surgery, chemotherapy, or radiotherapy of the pelvis were also excluded. Patients were randomized to treatment with preoperative radiotherapy consisting of 5 Gy on each of 5 days followed by TME, or to TME alone. Patients were followed postoperatively every 3 months during the first year and then annually for at least 2 years. This surveillance involved endoscopy and liver imaging with CT. In all, a total of 1861 patients were included, with 924 patients in the radiotherapy group and 937 in the surgery alone group. There were similar numbers of low anterior resections, Hartman procedures, and APRs between the two arms of the study.

The median interval between randomization and the date of surgery was 21 days in the radiation group and 14 days in the surgery alone group. The radiation group had a slightly higher intraoperative blood loss (1000 mL) compared with the surgery alone group (900 mL), a difference that was statistically significant ($p < 0.001$). Radiation therapy also increased the incidence of perineal complications compared with those not treated with radiation (26 versus 18%, $p = 0.05$). Local recurrence occurred in 87 total patients, of whom 52% had an isolated local recurrence, 32% had both local and distant disease, and 16% had a local failure after the diagnosis of distant metastasis. The local recurrence rate was 2.4% in the radiation group and 8.2% in the surgery alone group ($p < 0.001$). In multivariate regression analysis, treatment group assignment ($p < 0.001$), tumor location ($p = 0.03$), and TNM staging ($p < 0.001$) were independent risk factors for local recurrence, whereas the type of surgery ($p = 0.90$) was not. Further, univariate analysis revealed that preoperative radiotherapy reduced the risk of local recurrence in patients whose tumor was $\leq$ 5 cm from the anal verge, but not for cancers at other locations. Overall recurrence rates at the time of 2-year follow-up were 16.1% for the radiation arm and 20.9% in the surgery alone group ($p = 0.09$). Preoperative

radiation helped reduce recurrence in stage II and III cancers, but not in stage I and IV cancers. There was no interdependence between tumor location and treatment assignment or TNM staging and treatment assignment in multivariate subgroup analysis. Overall survival in the radiation group was 82% and in the surgery alone group it was 81.8% ($p = 0.84$), essentially the same. The rate of distant disease was 14.8% in the radiation group and 16.8% in the surgery alone group, which was a significant difference. At the conclusion of the follow-up period, 20% of the patients had died. Of the 365 patient deaths, 61 were postoperatively, 231 were cancer-related, and 70 were deemed unrelated to rectal cancer. Three patients had an unknown cause of death. The Dutch study demonstrated that preoperative radiotherapy combined with total mesorectal excision is beneficial for local control of disease, but does not effect overall survival despite a higher incidence of distant disease in the patients not receiving neoadjuvant radiotherapy. Although intraoperative blood loss was higher in the radiotherapy group, there was no significant increase in morbidity and mortality created by the addition of radiotherapy when compared with those not undergoing radiation treatments.

The German trial CAO/ARO/AIO-94[39] compared efficacy between neoadjuvant radiochemotherapy (RCT) with postoperative radiotherapy in patients undergoing TME for locally advanced (T3/T4 or node positive) disease. These patients were randomly assigned to pre- or postoperative RCT that involved a total dose of 50.4 Gy of radiation applied to the tumor and the pelvic nodes. Additionally, 5-FU (at 1000 mg/m^2/d) was given concurrently with radiotherapy during the first and fifth weeks as a 120-hour continuous infusion. Four other cycles of 5-FU were also administered, but in bolus form. RCT was identical in both treatment groups with the exception of a 5.4 Gy boost of radiation in the postoperative treatment arm. Patients in the postoperative arm underwent immediate surgery with chemotherapy beginning within 4 weeks postoperatively and comprising six cycles of 5-FU. In the preoperative RCT arm, surgery was performed 4 to 6 weeks after completion of preoperative RCT, with four cycles of 5-FU bolus treatments to begin within 3 to 4 weeks postoperatively.

Eight-hundred five patients were randomized from 26 different hospitals as of the first publication of the author's results. There were 355 patients in the neoadjuvant group and 363 in the adjuvant group. Toxicity most commonly involved diarrhea, with a 12% incidence of grade 3 toxicity in the neoadjuvant group and 11% in the adjuvant group. Fewer than 3% of patients in either arm experienced grade 3 erythema, nausea, or leukopenia. Postoperative complication rates were similar in both groups, with no difference in anastomotic leaks (12%) or postoperative bleeding (3%). There was also no difference in postoperative mortality between the treatment arms.

In summary, several well-designed large prospective studies have demonstrated that TME produces superior control of local recurrence as compared with conventional surgical techniques. On balance, morbidity with TME has not been significantly higher than with conventional surgery. At present, the benefit of TME appears to be additive with the effects of neoadjuvant radiotherapy rather than making the latter obsolete.

IMPACT OF TME AND PROBLEMS WITH ANASTOMOTIC LEAKS

Regardless of what name it is referenced by, total mesorectal excision is now the standard surgical approach to rectal cancer. Since its first descriptions, the ensuing discussion among surgeons and in training programs over what constitutes proper surgical technique for proctectomy with rectal cancer has led to a widely accepted and systematic approach to the surgery. This, in turn, has produced better oncologic outcomes compared with nonstandardized surgery, while maintaining acceptable morbidity and mortality rates. Several studies have described this phenomenon. In The Netherlands, the Dutch Colorectal Group compared[40] the short- and long-term outcomes of patients from their TME trial[38] with data from the older CRAB (cancer recurrence and blood transfusion) trial, which is an older study where the surgical technique for proctectomy was not closely controlled for. The study focused on those patients who were operated on with curative intent and without the benefit of neoadjuvant radiotherapy. The two studies were dissimilar with respect to gender, where the CRAB trial had more women and older patients, and more patients underwent postoperative radiotherapy. However, tumor location, types of resection performed, and tumor stage did not differ. Univariate analysis revealed that TME produced a higher incidence of anastomotic leaks, but this difference was not statistically significant on multivariate analysis. Local recurrence was improved in the TME trial (9 versus 16%), and the type of operation (conventional surgery versus TME) was found to be an independent predictor of overall survival ($p = 0.019$). Overall, there was a higher survival rate in the TME trial.

Law[41] reported similar findings in a review of 205 patients who underwent resection of rectal cancers that were ≤ 6 cm from the anal verge, with follow-up data collected prospectively. The authors reported that the incidence of APRs performed during the study decreased from 36 to 20% during the period of patient accrual. Five-year actuarial local recurrence rates favored double-stapled anastomoses (11.2%) compared with APR (23.5%). Overall, the 5-year survival rate in patients undergoing low anterior resection was 69.1%

compared with 51.1% in the APR group, although the difference was not statistically significant. Only 6 patients experienced an anastomotic leak.

Some series have reported higher leak rates[42] with TME, raising concerns that the improved oncologic results come at the price of higher leak rates. There are several likely reasons why TME has been associated with this complication. Interpretation of these reports is difficult as they are heterogeneous with respect to bowel preparation, whether a diverting stoma was used, anastomotic technique, whether pelvic drains were placed and what defined a leak in each study. Additionally, a review by Bruce et al[43] showed that 49 studies discussing anastomotic leaks used 29 different definitions to diagnose an anastomotic leak. One important factor in the observed increase in leaks is that patients undergoing total mesorectal excision are at risk for devascularization of the anorectal stump due to the low-level of many of these anastomoses and the subsequent removal of the distal mesorectum.[44] Many studies[45–47] have shown that low-lying anastomoses are at higher risk for leakage, perhaps functioning as a risk factor that is independent of the effects of total mesorectal excision. Eriksen[48] studied this issue in a prospective study of 1958 patients undergoing anterior resection with TME for rectal cancer from 1993 to 1998. The overall rate of leaks was 11.6% and multivariate analysis showed that the risk of leakage was significantly higher in men, in patients undergoing neoadjuvant radiotherapy, and in anastomoses that were ≤ 6 cm from the anal verge. The authors concluded that low anastomoses created after TME should be protected by a diverting stoma.

A variation on TME designed to decrease leak rates is the so-called partial mesorectal excision (PME), mentioned in the previously cited study by Law.[37] The idea involves resecting a healthy margin of mesorectum distal to the tumor to remove an appropriate margin of mesorectum particular to the location of the cancer. By not making total mesorectal removal obligatory in all rectal cancers, Law and others reported lower leak rates when the technique was used on more proximal rectal cancers. This idea may have merit, as studies[49] on resected rectal cancers have shown that the degree of distal cancer spread in the mesorectum is usually < 3 cm. The exact length of distal mesorectum required for control of cancer is unknown, but there has been a movement toward PME for tumors higher in the rectum. One technical aspect that is not mentioned in some studies using PME is the idea of avoiding narrowing the circumferential margin of dissection as it is performed distally. If the surgeon "cones" down the dissection, then too much of a distal mesorectal tail will be left and this will compromise control of the cancer. Although PME should be further studied, based on what we now know about the extent of distal cancer spread in the mesorectum, PME appears to be a valid technique to lower leak rates. It is likely that as a surgeon's experience with the technique increases, his or her leak rate will decrease, as illustrated by Carlsen's prospective study,[42] which documented this phenomenon in 76 patients undergoing TME.

FUNCTIONAL OUTCOME

TME has been associated with increased bowel frequency, fecal incontinence and urgency, with incidences that make these problems not uncommon.[50] Factors affecting postoperative bowel function include whether the patient experienced an anastomotic leak, the level of preoperative anorectal function, the type of anastomotic technique used, and the level of the anastomoses. Causal factors related to surgical technique are the impairment of continence caused by damage to the anal sphincter during dissection of the rectum, a smaller rectal capacity following proctectomy and possible sensory damage to the remaining rectum caused by damage to the pelvic nerves. Old age has often been regarded as a relative contraindication for anterior resection because of postoperative functional problems,[51] but a prospective study[52] of 87 patients undergoing TME and creation of colorectal anastomoses within 5 cm of the anal verge did not support this finding. The patients were divided into older (> 65 years) and younger (≤ 65 years) groups and were followed for a median of 24.1 months. This study showed no significant difference in continence, the number of bowel movements per day or urgency between the younger and older patients. Similar results have been seen in other studies.[53]

The use of adjuvant radiotherapy can cause postoperative deterioration of anorectal function after an anterior resection, as demonstrated by Kollmorgen and colleagues[54] in a comparison between 41 patients who received postoperative radiation and 59 patients who did not. The radiotherapy groups had a much higher median number of bowel movements per day compared with the surgery alone group (7 versus 2), a significantly higher rate of clustered bowel movements (42 versus 3%), and frequent incontinence (17 versus 0%). Liquid bowel movements were also more common in the radiated patients, which led to a higher incidence of perianal skin problems (41 versus 12%) and significant changes when comparing preoperative and posttreatment function between the two groups in the study (93 versus 61%).

Preoperative anorectal function may be predictive of postoperative functional outcome as suggested by Yamana et al.[55] This study followed 32 patients who underwent anterior resection for rectal cancer, and observed a postoperative decrease in rectal sensory threshold, anal mucosal electrosensitivity, and maximal tolerable rectal volume. No other functional differences were seen. The authors concluded that patients

who had a longer anal high-pressure zone, larger maximal tolerable rectal volume, and lower rectal sensory threshold had improved postoperative evacuator function.

AUTONOMIC NERVE PRESERVATION AND IMPACT ON URINARY AND SEXUAL FUNCTION

Identification and sparing of the autonomic pelvic nerves during proctectomy has been aided by the sharp dissection and precise technique of TME, resulting in well-preserved urologic and sexual function in the postoperative period with comparable control of disease. This is a marked departure from the surgeons who first described APR or low anterior resections, where male impotence was reported to approach 100%.[56] Havenga et al[57] reported on the results of 139 patients undergoing a nerve-sparing TME for cancer. The study was retrospective and based on questionnaire answers. Approximately 73% of male patients and 63% of female patients reported no urinary complaints after their surgery. The rest of the group reported one or more symptoms such as difficulty in bladder emptying, a feeling of incomplete bladder emptying, urgency, dribbling or urinary leakage. No patient required ongoing catheterization, however. The authors reported a higher incidence of these complaints in patients undergoing APR and receiving radiotherapy. Sexual activity was maintained in 86% of male patients under the age of 60 and in 46% of older patients. Comparing APR to LAR, sexual activity was maintained in 53 versus 76% of patients, respectively. The ability to maintain an erection was found in 86% of patients less than 60 and in 67% of patients older than 60. All 33 younger patients who underwent an LAR maintained their ability to engage in sexual intercourse with a spontaneous erection. Retrograde ejaculation was experienced in 20 to 40% of postoperative patients. Female patients had similarly good results, with 86% remaining sexually active after surgery. Ninety-one percent of the women were able to achieve orgasm and 85% were able to achieve arousal with vaginal lubrication.

Shirouzu at al[58] reported similar results in a review of 403 patients undergoing proctectomy over a 20-year time span, with some patients having a nerve-sparing approach and some not. With a 98% follow-up rate, nerve preservation did not increase recurrence rates or decrease 10-year disease-free survival rates when compared with the other group. Additionally, urinary and sexual function was better preserved in the nerve-sparing group. Urinary function was preserved in $> 80\%$ of patients with nerve preservation compared with $> 90\%$ of patients in the other group reporting urinary complaints. Likewise, 79% of the patients with nerve-preservation could maintain erection and 65% had preserved ejaculation.

Kim and colleagues[59] performed urinary flowmetry and used questionnaires to assess erectile dysfunction and prostate symptoms in 68 men who underwent nerve-sparing TME for rectal cancer. Comparing pre- and postoperative levels of function, nerve preservation resulted in maintained ability to achieve erection, penetration, antegrade ejaculation, sexual desire, intercourse satisfaction, orgasmic function, void volumes, and urinary flow.

NEOADJUVANT RADIOTHERAPY WITH TOTAL MESORECTAL EXCISION

Adequate doses of preoperative radiotherapy have been shown to reduce recurrence rates in comparison to surgery alone, although many of these studies had very high recurrence rates within the surgery alone[60] groups, suggesting a nonstandardized surgical approach was used. With the widespread application of TME, neoadjuvant radiotherapy has reduced local recurrence rates by as much as 50%. With a suboptimal resection, the impact of this reduction can be considerable, and though extremely controversial, may improve survival. In the Swedish Rectal Cancer Trial,[61] a short course of preoperative radiation therapy reduced local recurrence rates from 27% to 11% with a resultant increase in 5-year survival from 48 to 58%. When proper surgical technique with TME is used, however, the significance of reduction in local recurrence becomes considerably less and the survival benefit of neoadjuvant therapy cannot be reproduced. The Dutch Colorectal Cancer Group[38] achieved a local recurrence rate of 8.2% in the surgery alone group by adopting the principles of TME. The addition of preoperative radiation (25 Gy) further reduced the rate of local recurrence to 2.4%, but survival at 2 years was equivalent between the two groups. The current challenge is to develop better selection techniques for the use of neoadjuvant therapy so that oncologic benefit can be maximized while cost and complications are reduced. MRI is being used to determine the involvement of the radial margin (mesorectal fascia) and thus to select patients who would benefit from neoadjuvant therapy.[62–64]

Preoperative radiotherapy, like TME, offers the possibility of avoiding an APR by reducing the size of the tumor and allowing sphincter-preservation. This has spared many patients a permanent colostomy; however, caution must be used when considering a change in surgery based on tumor response to neoadjuvant therapy. Indeed, even after a complete response to neoadjuvant treatment, microscopic nests of malignant cells can be left behind in as many as 75% of patients.[65] Thus, the "melting" of the lesion does not change the true stage of the cancer and should not dissuade the surgeon from performing an APR when the cancer actually invades the sphincter muscle.

Short-term neoadjuvant radiotherapy can lead to higher rates of sexual dysfunction and result in a decrease in health-related quality of life (HRQL). Using the Rotterdam Symptom Checklist, Marijnen[66] and colleagues studied the HRQL and sexual function of 990 patients who underwent TME and were randomly assigned to either surgery alone or preoperative radiotherapy (PRT) with 25 Gy over 5 to 7 days. Patients filled out questionnaires preoperatively and at 3, 6, 12, 18, and 24 months after surgery. There was little difference in overall HRQL between the two groups, despite statistically significant reductions in daily activities in the PRT group. Patients who underwent PRT had slower resolution in defecation problems immediately after surgery, and PRT had a negative impact on sexual function in men and women. PRT had similar results in patients who had APR and LAR, with patients who had APR scoring better on their physical and psychological parameters, but with worse urologic function than those undergoing LAR.

Late side effects from PRT have also been studied, with the Dutch Colorectal Group[67] reporting that short-term PRT results in a higher incidence of long-term bowel dysfunction compared with the TME-alone group. Interestingly, urologic function did not differ between the two groups, nor did hospital treatment rates or stoma function. Patients in the radiotherapy arm reported a higher rate of fecal incontinence, the need to wear a pad, anal bleeding and mucous discharge.

DIFFERENT METHODS OF RECONSTRUCTION

After proctectomy, patients can have their intestine placed in continuity either with a straight colorectal (CRA) or coloanal (CAA) anastomosis, or by creating a neorectum with a coloplasty (CP) or a pouch. Each of these techniques has its learning curve and varying time requirements for proper construction. For patients who have normal anal sphincter function, the use of a colonic J-pouch has been shown[68,69] to provide better function than a straight coloanal anastomosis, and this benefit is apparent within one-year after surgery. These studies show that at 1 year over 80% of patients with pouch reconstruction have less than three bowel movements a day, whereas fewer than 40% of patients with CAA achieved this. Williams and Seow-Choen[70] provide a meta-analysis with equally impressive results; the studies with unison show that the pouch provides better functional outcomes than CAA, including reduced urgency rates and the reduced need for antidiarrheal medications. Their review also points out that leak rates may also be reduced with pouch reconstruction compared with a straight CAA, mentioning studies that demonstrated improved blood flow to the pouch-anal anastomosis based on laser Doppler flowmetry. Differences in blood flow may explain why Berger et al[69] reported leak rates as low as 3% in pouch patients while leak rates with straight CAA have been reported to be 5 to 15%.[70]

Ho et al[71] compared leak rates and functional results between colonic J-pouches and coloplasty-anal anastomoses in a series of 88 patients undergoing anterior resection for rectal cancer. Both groups were well matched. There was no difference in hospital stay or operative time, but CP resulted in higher leak rates. There was no difference in bowel function, continence scores, or quality of life at 1 year. In this series, CP resulted in higher leak rates, but without advantages in terms of postoperative function. Z'graggen et al[72] reported better results with CP in a series of 42 patients, approximately half of whom had proctectomy for cancer. A leak rate of 7% was recorded as well as a stool frequency that decreased to 2.1 per day by 8 months after surgery. After 6 months the incidence of stool urgency and incontinence decreased dramatically and no patient had ongoing difficulty with evacuation.

Remzi and colleagues[73] reviewed the complication rates, functional outcomes, and quality of life in patients undergoing a low anterior resection with an anastomosis at or below 3cm from the dentate line using reconstruction with a coloplasty ($n = 69$), a colonic J-pouch ($n = 43$), or a straight anastomosis ($n = 50$). Patients in each reconstructive group had comparable gender ratios and body mass indices. Overall, the only group of patients who experienced a higher incidence of anastomotic complications was those who had a hand-sewn colonic J-pouch; the other groups had no significant difference in leak rates. Overall, the patients with a straight anastomosis had a worse quality of life and functional outcome than did patients who underwent a coloplasty or colonic J-pouch. Coloplasty patients had quality of life outcomes that were equivalent to patients with a J-pouch based on the SF-36 questionnaire, and functional outcomes (the need for antidiarrheal medication, the need for constipation medication, the need for pads, clustering of bowel movements, incomplete evacuation, and urgency) were also equivalent.

In summary, the colonic J-pouch provides excellent early functional results compared with a straight CAA, and decreases daily stool frequency as well. The CP offers a rectal volume that lies somewhere between CAA and a J-pouch, and although tedious to create, offers results comparable to pouch formation. CP may be of most use in patients with a deep and narrow pelvis, where the creation of a pouch may not be feasible.

THE NEED FOR A DIVERTING STOMA

One answer to limiting the morbidity of an anastomotic leak is creating a diverting stoma. What leads a surgeon to decide on diversion is often the subjective feeling that

"the case was hard," but in the age of cost-containment there is a search for objective guidelines to help with this decision. Male gender, obesity, low (< 6 cm from the anal verge) anastomoses, tension, incomplete donuts, and possibly age have been cited as predictors of leaks. Koperna[74] performed a cost-effectiveness analysis that reviewed 70 consecutive patients undergoing anterior resection with ($n = 19$) and without ($n = 51$) a defunctioning stoma. Avoidance of a stoma resulted in significantly lower costs compared with patients who had a stoma. It was estimated that to balance the extra cost of a stoma, the anastomotic leak rate for LAR would have to be 16.5%. A suggested goal was to limit the stoma rate to $\leq 10\%$ of LAR's performed to limit the cost from associated with a stoma.

Dehni[75] compared leak rates in patients undergoing low colorectal (LCRA) and pouch-anal anastomoses. TME was performed for rectal cancer on 258 consecutive patients. A defunctioning stoma was placed in all 122 pouch patients and in 30 of the 136 LCRA patients. Clinical and radiological leak rates were tabulated. In LCRA patients without a stoma, the clinical leak rate was 17% compared with only 2 out of 30 of the LCRA patients with a diverting stoma. For patients with a pouch, the leak rate was 4.9%, which was not significantly different than the leak rate seen in diverted LCRA patients. The presence of a stoma also decreased the clinical severity of leaks and decreased the need for unscheduled surgeries to address the leak.

O'Leary et al[76] investigated quality of life issues in 24 patients undergoing LAR and loop ileostomy for rectal cancer compared with 23 patients undergoing LAR only for rectosigmoid cancers. Time to resume normal diet, hospital length of stay, and time to return to work were similar in both groups. However, at 12 weeks the group with a stoma had a reduction in physical conditioning scores on Short Form 36, which is a validated health survey questionnaire. This deficiency improved shortly after ileostomy closure. Factoring in ileostomy closure further increased total hospital stay and time away from employment compared with the group without a stoma. Closure of the ileostomy at the earliest appropriate time after proctectomy would help to limit some of these issues.

In summary, balancing the cost–benefit ratio would not allow using a stoma routinely as leak rates of experienced surgeons would make that unnecessary. When a patient does require a stoma, extra cost and time away from work can be limited by closing the stoma as soon as possible. This will also hasten the patients return to normal physical conditioning. Our practice is to use a diverting loop ileostomy if the anastomosis is within 6 cm of the anal verge or in cases where neoadjuvant therapy has been employed. We typically close the loop ileostomy at 3 months if a water-soluble contrast study of the anastomosis is normal.

CONCLUSION

Since becoming the standard surgical approach to proctectomy for cancer, TME has improved local control of rectal cancer through a dissection that removes the disease-bearing lymphatic tissue around the rectum and maintains fascial containment of the primary tumor. With experience, complications such as blood loss and anastomotic leaks are limited. At this time, neoadjuvant radiotherapy appears to be of continuing benefit despite the improvements in surgical technique.

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